2.5 mg of aluminum phosphate, 0.0125 mg of benzethonium chloride as a preservative, and is adjusted to pH 7.0. A 0.5 mL dose further contains up to 0.00000025 unit of penicillin, and 1 unit of streptomycin. The antibiotics are used in propagating polio virus for the manufacturing process and are thus present in only trace amounts.

The protamine sulphate is apparently present in the vaccine as an aid to the aluminum phosphate adsorption. All four components of the vaccine are adsorbed on the aluminum phosphate.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the primary immunization of infants beginning at an unstated age and children up to the age of 6 years against diphtheria, tetanus, pertussis, and poliomyelitis. An initial series of three 0.5 mL doses is recommended intramuscularly at 4- to 6-week intervals, followed by an additional dose of the quadrivalent product or poliomyelitis vaccine alone after 6 to 12 months. If immunization was begun in infants under 3 months of age, four 0.5 mL doses are recommended in the initial series.

b. *Contraindications.* No absolute contraindications are listed. Local and febrile reactions are noted, and the labeling advises that in instances of marked reactions, immunization may be completed with monovalent antigens, and warns that if there are encephalopathic symptoms, further injections of products containing pertussis vaccine are contraindicated.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* There is extensive documentation of the immunogenicity of the quadrivalent product in humans. The data obtained in the first major clinical trial was summarized by Barrett (Ref. 10). The lots used in this initial trial, however, were significantly substandard in potency of the pertussis component. Accordingly, a second major clinical trial was conducted in the years 1959 to 1960, using at various times both research and production lots of the quadrivalent product. These trials involved several hundred children, and a great deal of detailed data are provided to substantiate the immunogenicity in humans of all four components of this product.

In summary, there is substantial evidence of the human immunogenicity of all four components of this product when used as recommended.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* One study of the quadrivalent product is cited in the manufacturer's submission (Ref. 11) in which 851 children were studied, presumably in the course of primary immunization. There were 30 reactions possibly due to the immunization procedure, including 16 instances of tenderness at the injection site, 10 of fever, and 4 of rash. In the booster phase of the study, six instances of local or febrile reactions were reported. In another study of reactivity of the quadrivalent product, 50 children from Jamaica between the ages of 3 and 5 months were given an initial dose of 1 of 3 lots of this product. Although the criteria are not absolutely clear, 12 of the 50 children were described as having a significant local reaction, and 17 of the 50 children were described as having a significant systemic reaction. Eight children had erythema, 22 had induration, 11 complained of mild to moderate pain, none had severe pain, 19 had mild to moderate degrees of swelling, and 32 had some fever during the first 48 hours. No severe reactions were reported.

The submission (Ref. 11) further notes four instances of severe reaction, three of which included convulsions, reported during the years 1959 to 1963. A letter from a private physician, dated September 25, 1967, notes that physicians in the Boston area generally considered that the quadrivalent product had a higher frequency of minor reactions than was true of the trivalent product. In summary, however, adequate substantiation of the human safety of this product is provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This product is unique in that analysis of the producer's submission presents a strikingly different set of problems from those encountered with other diphtheria-pertussis-tetanus products. The submission clearly provides satisfactory evidence of safety and immunogenicity when used for primary immunization in humans.

Nevertheless, the last lot of this product was released in the year 1968, and the labeling is by now strikingly out-of-date with current practice and recommendations.

There is little doubt that there is still a role for killed poliomyelitis vaccine in selected patients, but there is clearly not a major role as long as live oral poliomyelitis vaccine remains an accepted part of public health practice in the United States. This product therefore exemplifies an ironic circumstance in which there is adequate documentation of safety and efficacy, yet little if any use in preventive medical practice.

5. *Recommendations.* The panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Poliomyelitis Vaccine Manufactured by Parke, Davis & Co.

1. *Description.* This unique quadrivalent product was designed to solve the stability problem that developed when DTP and killed poliomyelitis vaccine were mixed together in a single vial. This product consists of a dual chambered disposable syringe, preloaded with 1 dose each of killed poliomyelitis vaccine and DTP, adsorbed. For maximum stability the two components are physically separated in the preloaded syringe.

The composition of the DTP component is the same as Parke-Davis Quadrigen. The poliomyelitis component is concentrated in a 0.3 mL dose, and contains 8.3 mcg of formalin, less than 0.0000005 unit of penicillin, and less than 8.3 mcg of streptomycin. Benzethonium chloride 0.008 mg is added as a preservative.

2. *Labeling*—a. *Recommended use/indications.* Most of the labeling detailed the action of the preloaded double chambered bypass syringe. The recommended use and indications are otherwise the same as in the Quadrigen label.

3. *Critique.* All additional comments under labeling, analysis, critique, and recommendations are identical to those in the Parke-Davis Quadrigen submission and review (Ref. 12). This product has similarly not been released since the year 1968, and all discussion and recommendations about Quadrigen apply with equal validity to this product.

4. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Texas Department of Health Resources

1. *Description.* The product contains approximately 17.5 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid, and not more than the equivalent of 16 opacity units of pertussis per each

immunizing dose of 0.5 mL dose. The adjuvant is aluminum hydroxide, not to exceed 1.2 mg per mL, and the preservative is thimerosal 1:10,000. The total human immunizing dose contains 12 units of pertussis antigen.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for all infants for primary immunization, starting at 2 to 3 months of age. The initial course consists of three intramuscular injections given at not less than 1 month and preferably not more than 3-month intervals, followed by a reinforcing dose given about 12 months following the third dose. Injections are to be given intramuscularly preferably into the midlateral muscles of the thigh or the deltoid. In children over 6 years of age, the single antigens or tetanus and diphtheria toxoids adsorbed (for adult use combined antigen) is preferred. A routine booster of DTP is recommended at 3 through 6 years of age. For exposure recall, the tetanus toxoid fluid is recommended.

b. *Contraindications.* Any respiratory or acute infection is reason for delaying immunization.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The decline of the morbidity curves for diphtheria, tetanus, and pertussis in relation to introduction of vaccines in Texas is given as evidence of efficacy (Ref. 13). The Panel considers this evidence insufficient as proof of efficacy.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Since the introduction of this DTP vaccine in 1959 and the distribution of a few million doses, 17 reports of reactions have been received. The complaints have concerned fever but also contain the following report evidently from a single clinic: "High incidence of severe reactions; 20 to 30 percent of those immunized had severe reactions with cyst formation."

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization would be satisfactory if human efficacy is demonstrated and is satisfactory for booster immunization.

d. *Labeling.* The recommendations generally follow those of the Public Health Service Advisory Committee on Immunization Practices and are in general adequate except that there appears to be a misprint "tetanus and diphtheria toxoids absorbed" instead of adsorbed. The choice of fluid tetanus toxoid instead of adsorbed toxoid for exposure recall is questionable.

4. *Critique.* The major shortcoming is the lack of documentation of efficacy of this particular product; more specifically data on serologic response are lacking. The report of "20 to 30 percent of those immunized had severe reactions with cyst formation" (Ref. 13) requires some clarification.

Data on efficacy as reflected in serologic response are needed. Better observations could be made of vaccine reactions. Information on serological types of pertussis used in manufacturing may be of interest in view of recent data from Britain.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This product is a combination of purified tetanus and diphtheria toxoids and killed *Bordetella pertussis* cells adsorbed on aluminum phosphate adjuvant. The pertussis vaccine is prepared from strains providing serotype antigens 1 through 6 grown on a charcoal-agar modification of Cohen-Wheeler medium. The bacteria are killed and detoxified by heating at 56° C for 30 minutes. Each 0.5 mL dose of vaccine contains 7.5 Lf diphtheria toxiod, 5.0 Lf tetanus toxoid, and not more than 16 opacity units of pertussis vaccine. The preservative is thimorosal. The total human dose (1.5 mL) contains 12 antigenic units of pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization of infants and children through 6 years of age against diphtheria, tetanus, and pertussis. Recommendations for dosage and administration follow Public Health Services Advisory Committee on Immunization Practices' recommendations.

b. *Contraindications.* Defer use in acute respiratory infections or other active infections or during outbreaks of poliomyelitis. Immunization of infants with cerebral damage should be delayed until after 1 year and then single antigens in fractional doses should be employed. The occurrence of any type of neurological symptoms or signs after injection is said to be an absolute contraindication to further use.

3. *Analysis*—a. *Efficacy*—(1). *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data for this manufacturer's product were submitted. Claims for efficacy are baed on citations of relevant literature for this type of product (Ref. 14).

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data dealing with this product were submitted. No reference to marketing experience or complaint file information was included.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization would be satisfactory if human efficacy is demonstrated, and is satisfactory for booster immunization.

d. *Labeling.* The labeling is adequate and straightforward. It has not been revised since 1970, and could perhaps be updated slightly although no serious problems exist.

4. *Critique.* The submission (Ref. 14) is lacking in specific information relative to human safety and primary immunogenicity of this manufacturer's product. There is no basis for immediate concern at this lack of information but it should be obtained in due course.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions in accord with this Report are recommended.

The Panel also recommends that data on the reactogenicity of this specific product be collected and made available to the Bureau of Biologics.

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Generic Statement

Anthrax Vaccine, Adsorbed

Anthrax is an acute bacterial disease caused by *Bacillus anthracis*. The reservoir is any of several animal species (cattle, sheep, goats, horses, pigs) and the organism produces extremely resistant spores which may persist in soil and contaminate animals or their products. The disease is primarily an occupational hazard for industrial workers who process hides, hair (especially goat), bone meal, and wool, as well as for veterinarians and agricultural workers who may contact infected animals.

Most infections are cutaneous; if untreated they may spread to regional lymph nodes and may cause a fatal septicemia. Primary inhalation and gastrointestinal infections do occur, but with low frequency, and are highly fatal.

Description of Product

Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonproteolytic, nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*. It contains no more than 0.83 mg aluminum per 0.5 mL dose, 0.0025 percent benzethonium chloride as a preservative, and 0.0037 percent formaldehyde, which is believed to act as a stabilizer.

The product is tested according to the Public Health Service regulations for biological products and specific additional standards for anthrax vaccine. In addition to tests for general safety and sterility, the product is subjected to a potency assay of its protective activity in guinea pigs, which are challenged with virulent *Bacillus anthracis*.

Indications and Contraindications

Immunization with this vaccine is indicated only for certain occupational groups with risk of uncontrollable or unavoidable exposure to the organism. It is recommended for individuals in industrial settings who come in contact with imported animal hides, furs, wool, hair (especially goat hair), bristles, and bone meal, as well as laboratory workers involved in ongoing studies on the organism.

Contraindications to its use include:

1. A history of clinical anthrax infection which may enhance the risk of severe reactions.

2. Severe systemic reactions with marked chills and fever following a prior injection—in this case further attempts at immunization should be abandoned.

3. The presence of acute respiratory disease or other febrile illnesses in order not to confuse the cause of further fever.

4. Therapy with corticosteroids or other immunosuppressive agents—in this case immunization should be deferred until such therapy is completed. If on long-term therapy, a more intensive immunization schedule should be considered.

Safety

In general, safety of this product is not a major concern, especially considering its very limited distribution and the benefit-to-risk aspects of occupational exposure in those individuals for whom it is indicated. Local reactions are typically mild, with erythema and slight local tenderness for 24 to 48 hours. Some individuals may have more severe local reactions with edema, erythema greater than 5 x 5 cm, induration, local warmth, tenderness, and pruritus. Only a few systemic reactions with marked chills and fever have been recorded. All reactions reported have been self-limited.

Efficacy

The best evidence for the efficacy of anthrax vaccine comes from a placebo-controlled field trial conducted by Brachman (Ref. 1) covering four mills processing raw imported goathair into garment interlinings. The study involved approximately 1,200 mill employees of whom about 40 percent received the vaccine and the remainder received a placebo or nothing. The average yearly incidence of clinical anthrax in this population was 1 percent. During the evaluation period, 26 cases of anthrax occurred. Twenty-one had received no vaccine, four had incomplete immunization and one had complete immunization. Based on analysis of attack rates per 1,000 person-months, the vaccine was calculated to give 93 percent (lower 95 percent confidence limit=65 percent) protection against cutaneous anthrax based on comparison with the control group. Inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease.

The Center for Disease Control has continued to collect data on the occurrence of anthrax in at-risk industrial settings. These data were summarized for the period 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of this product.

Special Problems

Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented. This question is not amenable to study due to the low incidence and sporadic occurrence of the disease. In fact, the industrial setting in which the studies above were conducted is vanishing, precluding any further clinical studies.

In any event, further studies on this vaccine would receive low priority for available funding.

Recommendations

The Panel believes that there is sufficient evidence to conclude that

anthrax vaccine is safe and effective under the limited circumstances for which this vaccine is employed.

Reference

(1) Brachman, P. S., H. Gold, S. A. Plotkin, R. Fekety, M. Werrin, and N. R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," *American Journal of Public Health*, 52:632–645, 1962.

SPECIFIC PRODUCT REVIEW

Anthrax Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* Anthrax vaccine adsorbed is an aluminum hydroxide adsorbed preparation of protective antigen of *Bacillus anthracis.* The product is prepared from a sterile filtrate of a microaerophilic culture of an avirulent, nonproteolytic, nonencapsulated strain. The product contains 0.83 mg of aluminum per single human dose (0.5 mL) and is preserved with 0.0025 percent benzethonium chloride. Not more than 0.0037 percent formaldehyde is added as a stabilizer.

2. *Labeling*—a. *Recommended use/indications.* This product is intended solely for immunization of high-risk of exposure industrial populations such as individuals who contact imported animal hides, furs, bone meal, wool, hair (especially goat hair), and bristles. It is also recommended for laboratory investigators handling the organism. Primary immunization consists of 6 subcutaneous 0.5 mL injections at 0, 2, and 4 weeks and 6, 12, and 18 months. Subsequent boosters at yearly intervals are recommended.

b. *Contraindications.* Prior anthrax infection is an absolute contraindication. Immunization should be avoided in acute respiratory disease or other active infections. Corticosteroid therapy may suppress response. Further immunization should be discontinued in those rare individuals who suffer severe systemic reactions.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* **This product meets Federal requirements.**

(2) *Human.* The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman (Ref. 1) in a placebo-controlled field trial in mills processing imported goat hair. This vaccine appeared 93 percent protective (lower 95 percent confidence limit=65 percent protective) against cutaneous anthrax. No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence. The Michigan Department of Public Health vaccine is patterned after that of Merck Sharp & Dohme with various minor production changes. It has been distributed by the Center for Disease Control since 1966, first as an investigational new drug and since 1972 as a licensed product. A review of the Center for Disease Control data pertinent to this product for the period 1962 to 1974 in at-risk industrial settings indicates that no cases have occurred in fully immunized workers (see Generic Statement).

b. *Safety*—(1) *Animal.* **This product meets Federal requirements.**

(2) *Human.* Accumulated data for the Center for Disease Control suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare.

c. *Benefit/risk ratio.* This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory under the prevailing circumstances of use.

d. *Labeling.* **The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24(a) (21 CFR 620.24(a)) defines a total primary immunizing dose as 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months).**

4. *Critique.* **This product appears to offer significant protection against cutaneous anthrax in fully immunized subjects. This is adequately established by the controlled field trial of the very similar Merck Sharp & Dohme experimental vaccine and by the Center for Disease Control surveillance data conducted on industrial high-risk settings.**

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Reference

(1) Brachman, P. S., H. Gold, S. A. Plotkin, R. Fekety, M. Werrin, and N. R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," *American Journal of Public Health*, 52:632–645, 1962.

Generic Statement

BCG Vaccines

Tuberculosis is a communicable disease of world-wide importance caused by *Mycobacterium tuberculosis.* The disease typically involves the lungs, but is capable of causing disease in any organ system of the body. The World Health Organization estimates the number of infectious cases of tuberculosis in the world today to be in the range of 15 to 20 million.

Tuberculosis has declined sharply in the United States during the past several decades. United States Public Health Service data indicate that in 1953 there were 84,000 new cases of tuberculosis and 19,700 deaths due to tuberculosis; in 1977 there were only 31,145 new cases and the number of tuberculosis deaths had declined to 3,000. Factors contributing to the observed decline in tuberculosis morbidity and mortality include the gradual increase in socioeconomic level that has characterized the U.S. economy, improved nutrition, the introduction of effective chemotherapy of active tuberculosis, and the increasing use of isoniazid in preventive therapy. There remain, however, localized foci or "pockets" of tuberculosis transmission in the United States, particularly in areas in which preventive medical services are suboptimal or cannot be adequately delivered.

In many other countries, the use of BCG vaccine is credited with a major role in reducing tuberculosis morbidity. BCG vaccination has been the major thrust of the World Health Organization's efforts to control tuberculosis in countries with high rates of transmission of the disease. Although available in the United States, this product has been used but little for the prevention of tuberculosis.

BCG vaccines posed a particular problem for the Panel, owing to the widely disparate results of controlled field trials, and the lack of a reproducible animal model which accurately reflects protective efficacy in humans.

1. *Rationale for vaccination against tuberculosis.* Earlier in this century, a large majority of people became infected with tubercle bacilli as demonstrated by skin test positivity. However, only a small proportion of those who were infected developed overt tuberculous disease. Most people who were infected appeared to have acquired a degree of resistance against developing overt tuberculosis upon subsequent exposure, which, earlier in this century, was frequent and virtually unavoidable.

Immunity in tuberculosis is now much more easily understood in terms of modern immunologic concepts, and the "unitary concept" of the pathogenesis of tuberculosis in man is generally accepted. Thus, primary infection with tubercle bacilli results in specific sensitization of host cell-mediated immune mechanisms, and is reflected clinically in the ability to elicit a positive tuberculin skin test. If the primarily infected person has received a large dose of tubercle bacilli, or if his cell-mediated immune mechanisms do not, for one reason or another, respond optimally, the individual may go on to develop overt clinical tuberculosis. Most frequently, however, the tuberculous infection is localized by the host cell-mediated immune mechanisms, resulting in a dormant or latent infection which may (a) remain dormant for life, or (b) disappear and reactivate at some time in the future. Reactivation is frequently but not invariably associated with conditions known to impair host cell-mediated immune mechanisms, such as immuno-suppressive therapy, certain malignancies, or malnutrition.

There is abundant clinical and experimental evidence that tuberculin positivity, reflecting activated cell-mediated immune mechanisms, is associated with protection against exogenous exposure to tuberculosis. Such individuals are, however, at risk of reactivation or "breakdown" tuberculosis. Tuberculin negative individuals are susceptible to primary infection, but by definition are not at risk of "reactivation" tuberculosis. The disease may be spread by individuals with primary infection, reinfected susceptible individuals, or those with reactivation tuberculosis.

The use of BCG vaccine, an attenuated strain immunologically closely related to virulent *Mycobacterium tuberculosis,* attempts to gain the advantage of protection conferred by activated host cell-mediated immune mechanisms without risking progressive disease in man.

2. *History of BCG vaccine.* The bacillus of Calmette and Guerin, known as BCG, was originally derived from a virulent strain of *Mycobacterium bovis,* attenuated by 231 serial passages over a period of 13 years on beef-bile-containing medium. The early studies of Calmette and Guerin indicated that animals immunized with this culture developed increased resistance to a challenge dose of virulent tubercle bacilli. BCG vaccine was first administered by mouth to newborn infants in 1921. Since then the vaccine has been administered to more than 500 million persons of all ages.

The organism was maintained by serial passage at the Pasteur Institute, and in the decades following its description, was subcultured and distributed to hundreds of laboratories in many countries. In those laboratories, many of which produced their own BCG vaccines, the strain was similarly maintained by serial subculture. It became apparent in the mid-1950's that serial subculturing in many different laboratories on differing media had resulted in the production, by inadvertent selection, of many different "daughter" BCG strains which differed, sometimes widely, in gross morphology, growth characteristics, biochemical activity, sensitizing potency, and even animal virulence. Nor was it possible, of course, to carry out direct comparisons of any of the BCG "daughter" strains to the original bacillus of Calmette and Guerin. In the last two decades most production laboratories producing BCG vaccine have adopted a seed lot system, maintaining production strains in a lyophilized state, in an attempt to minimize the genetic variation that is unavoidable in serial subculture. The production strains are generally named by the city in which the production laboratory is located, e.g., Paris, Copenhagen, London, Montreal, Rio de Janeiro, etc. Thus, there is no single BCG vaccine; there are, rather, dozens of different BCG "daughter" vaccines.

Description and Production of BCG Vaccine

The proper name of this product is BCG vaccine, and consists of a freeze-dried preparation containing live bacteria of the bacillus of Calmette and Guerin, an attenuated strain of *Mycobacterium bovis.* The Strain must have been maintained in the form of a primary seed lot, the basic material from which secondary seed lots are prepared. Vaccine production may be either from primary or secondary seed lots. The source of the strain used in vaccine manufacture is not specified in current Federal requirements, which state only that the source of the vaccine shall be identified by complete historical records.

In most production laboratories, the bacilli are grown as a pellicle on the surface of liquid Sauton medium, or dispersed throughout Sauton medium. An early harvest, 6 to 9 days, is considered important for good survival after freeze-drying. After filtering and pressing, the semi-dry mycobacterial mass is homogenized at a controlled temperature, diluted, and subsequently freeze-dried.

Routine quality control carried out by production laboratories includes an identity test, test of contamination, safety test in guinea pigs, estimate of total bacillary mass by opacity and dry weight, viability determined by oxygen uptake, germination rate, or colony count, and tests of heat stability. Such routine tests are particularly important for ensuring batch-to-batch uniformity.

The Panel is cognizant of the proposed new standards for BCG vaccine published in the **Federal Register** of March 18, 1974 (39 FR 10158–10160). These standards define the necessity of demonstrating that production lots of BCG vaccine are incapable of producing progressive tuberculosis in guinea pigs, and induce tuberculin skin test positivity using 5 to 10 units of tuberculin purified protein derivative (PPD) in 90 percent of persons, previously tuberculin negative, given BCG vaccine. In addition to the clinical requirement for tuberculin skin test conversion, potency testing is required by a determination of the number of colony forming units, and the intradermal guinea pig test (Jensen's test). (Note: In the **Federal Register** of March 13, 1979 (44 FR 14541), FDA issued final standards for BCG vaccine based on its proposed regulations issued March 18, 1974.)

Indications and Contraindications

This has long been a controversial issue in the United States. The recommended use of BCG vaccine is to prevent tuberculosis, but controversy has arisen when attempts were made to define the groups of individuals or populations that would benefit from BCG vaccination.

The recently published recommendations of the Public Health Service Advisory Committee on Immunization Practices with regard to BCG vaccines read as follows (Ref. 1):

> Thorough application of modern methods of case detection, chemotherapy, and preventive treatment can be highly successful in controlling tuberculosis. Nevertheless, an effective BCG vaccine may be useful under certain circumstances. In particular, BCG may benefit uninfected persons with repeated exposure to infective cases who cannot or will not obtain or accept treatment.
>
> *Specific recommendations*—a. BCG vaccination should be seriously considered for persons who are tuberculin skin-test negative and who have repeated exposure to persistently untreated or ineffectively-treated, sputum-positive pulmonary tuberculosis.
>
> b. BCG vaccination should be considered for well-defined communities or groups if an excessive rate of new infections can be demonstrated and the usual surveillance and treatment programs have failed or have been